Kidney International, Vol. 44 (1993), pp. 1322–1326

Incidence and risk factors for hepatitis C seroconversion in hemodialysis: A prospective study

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Incidence and risk factors for hepatitis C seroconversion in hemodialysis: A prospective study. To delineate the incidence and risk factors for seroconversion (SC) for HCV, from May 1991 to November 1992 we followed all 401 patients (no i.v. drug abusers) dialyzed in 15 Belgian hemodialysis (HD) units, none of which isolates anti-HCV (+) patients. The sensitive ELISA II test was performed in the same laboratory for all patients. ELISA II (+) sera were considered truly positive if specific antibodies were detected by RIBA II against at least one HCV antigen. Blood transfusions given from 12 months prior to inclusion in the study, dialyzer reuse and frequency of dialysis monitor sterilization were recorded. In May 1991, prevalence of truly positive ELISA II tests averaged 13.5% (54/399). During the three consecutive six-month periods, ELISA II became truly positive in 3 of 305 (1%), 4 of 314 (1.3%) and 1 of 313 (0.3%) patients, respectively, which was an average yearly incidence of 1.7%. SC was preceded (1 to 6 months) in all cases by an unexplained, unprecedented increase in the alanine aminotransferase level. The mean monthly rate of transfusions was significantly higher ($P < 0.001$) in eight patients with SC (0.7 ± 0.6 U) than in 393 patients without SC (0.1 ± 0.01 U). However, three of eight patients with SC had not been transfused at all. SC was observed in only 3 of 13 units (1, 3 and 4 cases, respectively) dialyzing ELISA (+) patients. In the unit with three SC, patients were always assigned a fixed station: SC was observed only in patients dialyzed next to an ELISA II (+) patient (3 of 8 vs. 0 of 30, $P < 0.02$). These facts suggest nosocomial transmission. SC was not associated with dialyzer reuse or the lack of sterilization of the dialysis monitor after each session. In conclusion, the yearly incidence of SC (ELISA II) averaged 1.7% in our group of hemodialyzed patients. Contamination appeared to be both transfusional and nosocomial. The absence of SC in 10 of 13 units dialyzing ELISA (+) patients suggests that isolation of such patients is not yet warranted. Strict adhesion to the "universal precautions" (CDC, Atlanta) is probably sufficient to prevent nosocomial transmission. Further long-term studies are needed to confirm these conclusions.

Infection by the hepatitis C virus (HCV) is frequent in hemodialyzed patients [1–4], and worrysome as it often becomes chronic and induces chronic liver disease [5, 6]. Its prevention is therefore a major challenge for nephrologists.

We report on an 18-month prospective multicenter study undertaken to assess the incidence [as expressed by the seroconversion (SC) rate] and the risk factors for HCV infection in hemodialyzed patients.

Methods

Design of the study

A blood sample was obtained from all patients on chronic hemodialysis (HD) in 15 Belgian units, every six months from May 1991 to November 1992.

Hemodialyzed patients

In May 1991, 402 patients were included. They had been dialyzed for 1 to 257 (median 26) months. Their age ranged from 13 to 89 (median 61) years.

In November 1991 and May 1992 an additional 60 and 61 patients were included, respectively. Of these 121 patients, 117 had recently started HD, one resumed HD after a failed transplantation and three had been transferred from other units. Their age range was similar to that of the previously included patients.

In November 1992, an additional 76 patients, recently started on HD, were included. Their age range was similar to that of the previously included patients. This last group completed the assessment of the prevalence of HCV antibodies in patients recently started on HD as well as of the prevalence of HCV antibodies in the whole study group from May 1991 to November 1992.

Hemodialysis units

Fifteen collective HD units (hospital $N = 14$, low-care $N = 1$) participated in the study. None of these units isolated patients with HCV antibodies. Patients on home HD were not included.

Serologic tests for HCV antibodies

All blood samples were tested by the Virology Laboratory of the University Clinics St-Luc. Samples were centrifuged and serum stored at −80°C until testing.

The sensitive second generation ELISA test for HCV [2, 7–9] (Ortho HCV ELISA 2.0, further called ELISA II, Ortho

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Received for publication April 19, 1993
and in revised form July 20, 1993
Accepted for publication July 22, 1993

Diagnostic Systems, Raritan, New Jersey, USA) was performed on all serum samples, according to the manufacturer's instructions. This test detects antibodies directed against both non-structural (C200, a composite of C100-3 and C33) and structural (C22 = core) HCV antigens. A serum was considered as ELISA-positive only if repeat testing proved positive.

All ELISA-positive sera were tested by second generation Recombinant ImmunoBlot Assay [10, 11] (RIBA II, Ortho Diagnostic Systems). In this test four HCV recombinant antigens (C100-3, 5-1-1, C33, C22) and superoxide dismutase were blotted as separate bands on a nitrocellulose strip. After incubation with the patient's serum, the presence of specific antibodies was revealed by a goat antihuman IgG antibody conjugated with a peroxidase.

In this study the ELISA II test was taken as truly positive if specific antibodies were detected against at least one HCV antigen by the RIBA II test. Indeed, in most HD patients with such a RIBA II pattern, HCV-RNA can be demonstrated in serum by the polymerase chain reaction [12]. The few ELISA II (+) patients with a non-reactive RIBA II were excluded from the calculations of incidence and prevalence.

Risk factors for SC for HCV

Blood transfusions were recorded for each patient. As infection may precede SC by up to 12 months [9], the listing included transfusions given from 12 months prior to inclusion up to the end of the study.

All blood derivatives able to transmit viral infections (red cells, whole blood, plasma, platelets) were recorded. Pasteurized albumin solutions were excluded [13].

The existence of a history of intravenous drug abuse (IVDA) and the presence of antibodies against human immunodeficiency virus (HIV) were specifically checked by a questionnaire to the referring nephrologists.

Dialyzer reuse and the frequency of dialysis monitor sterilization were recorded.

Sexual partners of patients who seroconverted were tested by ELISA II.

Statistics

Results are expressed as mean ± SEM as indicated. Unpaired Student's t-test, χ^2 and Fisher's exact test were used as indicated. P values < 0.05 were considered as significant.

Results

Prevalence of ELISA positive patients at the time of inclusion

The ELISA II test was initially positive in 57 of 402, 3 of 60, 3 of 61 and 6 of 76 patients included in May 1991, November 1991, May 1992 and November 1992, respectively. The presence of specific anti-HCV antibodies was detected by RIBA II in 54 of 57, 1 of 3, 3 of 3 and 6 of 6 cases, respectively (Table 1). In May 1991, the prevalence of truly positive ELISA II patients ranged from 0 to 31% in the 15 participating units.

Adequacy of serologic follow-up

Out of 523 patients included in May 1991, November 1991 and May 1992, 158 did not complete the study as a result of death ($N = 93$), renal transplantation ($N = 50$), transfer to other dialysis units ($N = 11$), recovery of renal function ($N = 3$), or transfer to peritoneal dialysis ($N = 1$). Of the total of 1679 expected serum samples, only six (0.36%) were missing, all in seronegative patients who remained so at later follow-up.

Table 1. Prevalence and incidence of truly positive ELISA II tests

	May 1991	November 1991	May 1992	November 1992
Prevalence in new patients	—	1.7% (1/60)	5% (3/61)	8% (6/76)
Prevalence in the whole group	13.4% (54/399)	12.4% (51/410)	12.2% (51/419)	11.8% (51/433)
Incidence/6 months	—	1% (3/305)	1.3% (4/314)	0.3% (1/313)

Note that ELISA II (+) tests non-reactive by RIBA II were excluded from the calculations.

Incidence of SC for HCV

During the three consecutive six-month periods, three, five and one patient, respectively, became ELISA (+). In eight patients specific reactivity was detected by RIBA II against HCV antigen(s) including C33 in seven of eight cases. In the ninth patient, suffering from multiple myeloma, the RIBA II test (May 1992) was non-reactive; the false positive ELISA was ascribed to the paraprotein [14]. The six month incidence of true SC was thus 3 of 305 (1%), 4 of 314 (1.3%) and 1 of 313 (0.3%), respectively, which is an average of 1.7% per year. We further calculated the SC rate in all ($N = 193$) patients already on HD for six months in May 1991 and followed throughout the 18 month study; five SC were observed for an average yearly incidence of 1.73%, thus identical to that observed in the whole group.

Alanine aminotransferase (ALT) level in patients who seroconverted

ALT determinations obtained every one to two months from the onset of HD were reviewed in the eight patients with true SC. In each case, SC was preceded (1 to 6 months) by an unexplained, sustained elevation of the ALT level (>6 weeks duration, at least 2—mean: 5—ALT results above the upper limit of normal values). This rise was not accounted for by hepatitis B virus infection or hepatotoxic drugs, and was noted for the first time since the initiation of HD.

Risk factors for SC for HCV

The mean monthly rate of blood transfusions was significantly ($P < 0.001$, unpaired t-test) higher in the eight patients with SC (0.7 ± 0.6 unit) than in patients without SC (0.1 ± 0.01 unit).

It is noteworthy that two patients exclusively received ELISA I negative blood units whereas three patients had not been transfused at all after May 1, 1990.

SC were observed in only three of the 15 participating units (1, 3 and 4 cases, respectively). In May 1991 these three units treated 34% of the patients. Initial prevalence of truly positive ELISA II patients averaged 16.3% (22 of 135), a value similar to the 12.6% (32 of 253) observed in the 10 other units with ELISA (+) patients. The proportion of ELISA II (+) patients in whom

Table 2. Risk factors for seroconversion (SC) for HCV

	SC (N = 8)	No SC (N = 393)	P value
Transfusions			
Mean number ± SEM of units/month	0.7 ± 0.6	0.1 ± 0.01	<0.001
Number of patients not transfused	3/8	180/393	NS
Number of patients transfused with ELISA I negative units only	2/8	NA	
i.v. Drug abuse (number of patients)	0	0	
Dialyzer reuse (number of treated patients)	3/8	158/393	NS
Sterilization of dialysis monitor after each session (number of treated patients)	3/8	88/393	NS

Abbreviations are: NS, not significant; NA, not available.

RIBA II detected antibodies against ≥2 HCV antigens was similar in the three units with (18 of 22) and in the 10 units without (27 of 32) SC.

In the unit with three SC, patients (N = 38) were always assigned the same station. The prevalence of SC was significantly higher (3 of 8) among patients dialyzed next to an ELISA II positive patient than among the others (0 of 30; $P < 0.02$, Fisher's exact test).

No patient included in the study was an i.v. drug abuser or had antibodies against HIV.

Incidence of SC was not associated with dialyzer reuse or lack of sterilization of dialysis monitor after each session (Table 2).

We tested the sexual partners of four patients with SC. ELISA II proved negative in all. No partner was identified in three widowed patients, whereas one partner was lost to follow-up.

Serologic follow-up of ELISA positive patients

All truly positive ELISA II patients (N = 56) remained ELISA II (+) throughout follow-up (68 patient-years).

Evolution of the prevalence of truly positive ELISA tests over the study period

Over the 18 months' study period, the overall prevalence of truly positive ELISA II tests decreased slightly from 54 of 399 (13.4%) in May 1991 to 51 of 410 (12.4%) in November 1991, 51 of 419 (12.2%) in May 1992 and 51 of 433 (11.8%) in November 1992 (Table 1).

Discussion

Our study defined prospectively the SC rate for HCV with the sensitive ELISA II in a large series of 401 HD patients. The SC rate averages 1.7% per year. The recent infection by HCV of the patients with SC is confirmed by a recent, unprecedented, ALT level increase in each patient and a RIBA II pattern with predominant anti-C33 antibodies compatible with recent SC [15].

Previous data on this subject were limited to a large retrospective study and three small prospective studies. Dentico et al [16] using a less sensitive ELISA I test reported in 115 Italian HD patients, a yearly incidence of SC for HCV falling from 6.1 to 2.2% between 1984 and 1990. Unfortunately, this retrospective study relied on frozen sera available in only less than half the population at risk. In the absence of information on the reason why sera were available for some patients and not for others, these results are open to question. Two small prospective studies relying on the ELISA I test in 35 and 48 HD patients followed for 12 months, reported a yearly incidence of 11.4% (Saudi Arabia) [6] and 6% (France) [17], respectively. These figures are probably underestimates of the actual incidence in these populations as the sensitivity of the ELISA I test is only 54 to 76% of that of the ELISA II test in HD patients [2, 7, 8, 18]. More recently, a prospective study relying on the second generation assay reported a yearly incidence of 4.9% in 39 HD patients followed in Hong Kong for 19 months [18].

Our study confirms that blood transfusions are a risk factor for the transmission of HCV in HD [1, 3, 4]. The small decrease in the prevalence of truly positive ELISA II patients observed in our series probably reflects the reduction in transfusion requirements due to the introduction of erythropoietin treatment in Belgium by mid-1989 as well as the screening of blood units initiated in Belgium with ELISA I in May 1990 and with ELISA II in August 1991.

However, factors other than transfusion contribute to the transmission of HCV as demonstrated by the absence of blood transfusions in three of the eight patients with SC. Neither sexual transmission nor IVDA can be incriminated—indeed, the four sexual partners tested were ELISA II negative (including the partners of 2 nontransfused patients with SC) and no patient was an IVDA. Interestingly, other studies have detected HCV antibodies in up to 19 to 39% of HD patients never given a blood transfusion [4, 19, 20].

These facts taken together with the clustering of SC in three units point to the possibility of a nosocomial transmission. This hypothesis is supported by our observation that patients dialyzed in a bed adjacent to that of an ELISA (+) patient had a significantly higher risk of SC than the others in the same unit.

To prevent nosocomial transmission, several groups have advocated the segregation of HCV(+) from HCV(−) patients [4, 20, 21]. This recommendation is questionable as its effectiveness is unknown and its implementation difficult.

Effectiveness is limited by the up to one year delay between HCV infection and the detection of antibodies by the ELISA II test [9]. Admittedly, new tests [5, 22] will probably decrease this delay and improve the detection of HCV infection. Furthermore, the possibility of a lack of cross immunity between different strains of HCV must be borne in mind. Indeed, unlike the hepatitis B virus, the HCV exhibits a major genomic variability [23] and it has recently been demonstrated that sequential inoculation of convalescent chimpanzees with different HCV strains results in the reappearance of viremia due to infection with the last inoculated strain [24]. This concern has led some transplantation units to refuse to transplant ELISA + organs in ELISA + recipients [25]. Grouping of ELISA + patients in dialysis units might thus increase their risk of acquiring multiple HCV strains.

Implementation of a rigorous separation between patients according to their HCV status is rather cumbersome. In units also treating HBsAg positive patients, this would imply up to four separate facilities (B+C+, B+C−, B−C+ and B−C−)!

The German Association of Clinical Nephrologists has recently recommended isolating only ELISA II (+) patients with ALT levels higher than the double of the upper limit of normal

[26]. This proposal fails to consider that many HD patients have normal ALT values despite the fact that they are infective as demonstrated by a positive polymerase chain reaction for HCV-RNA [18].

Our observations suggest that isolation of ELISA + patients is not mandatory to prevent nosocomial HCV transmission in HD units. Indeed no SC for HCV was observed over 18 months in 10 of 13 units dialyzing ELISA (+) together with ELISA (−) patients. As the highest prevalence among participating units was 31%, our data do not permit definition of the risk of nosocomial HCV infection in units with an even higher prevalence. Interestingly however, no SC was observed throughout the study in the unit with a 31% prevalence. The lack of seroconversion in 10 units is not accounted for by a lower prevalence of ELISA II positive patients. A lower infectivity of ELISA (+) patients in these 10 units appears equally unlikely as the RIBA II pattern [10, 11] was similar in units without and with SC. Similarly, there was no difference in dialyzer reuse or frequency of dialysis monitor sterilization between units without and with contamination. The most likely remaining explanation to be considered is that measures to prevent cross-contamination were better observed in the units without than in units with SCs. Such measures are detailed in the "universal precautions for prevention of transmission of blood borne pathogens in health care settings" [27] and "recommended precautions for patients undergoing hemodialysis who have AIDS or non-A non-B hepatitis" [28] delineated by the Center for Disease Control (Atlanta, Georgia, USA). They include cleaning and disinfection of instruments, machines and environmental surfaces that are routinely touched, avoidance of sharing of articles between patients, frequent handwashing and use of gloves! A recent outbreak of HCV infection in a HD unit was effectively controlled by the implementation of these simple, too often neglected measures [29].

In conclusion, the yearly incidence of SC for HCV (ELISA II) averages 1.7% in our prospective study in HD patients.

Contamination appears to be both transfusional and nosocomial. The absence of SC in most units dialyzing ELISA + patients suggests that isolation of such patients is not yet warranted. By contrast, strict adhesion to the "CDC guidelines" is recommended. Further long-term studies are needed to confirm these conclusions.

Acknowledgment

This study was presented in part orally at the American Society of Nephrology, Baltimore, Maryland, November 1992.

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